Exhibit G.

Hemodynamic ben fits and prolonged survival with long-term captopril therapy in rats with myocardial infarction and heart failure

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ABSTRACT To determine whether the hemodynamic profile of chronic heart failure secondary to myocardial infarction could be altered, captopril was administered to female Wistar rats 3 weeks after coronary artery ligation and continued for 3 months. Captopril reduced left ventricular mass, prevented the increase in right ventricular mass observed with increasing infarct size, lessened the increase in left ventricular end-diastolic pressure, and reduced mean arterial pressure and total peripheral resistance, whereas cardiac output and heart rate were maintained. The end-diastolic volume of treated rats with moderate infarcts was significantly less than that of untreated rats, and therefore the ejection fraction index was significantly increased. In rats given captopril until death or for a period of up to 1 year, survival was significantly prolonged, particularly in those rats with moderate-sized infarcts.
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CORONARY ARTERY LIGATION in the rat provides an animal preparation of myocardial infarction for the study of the effects of a discrete loss of myocardium on global ventricular performance and survival. Previous studies have demonstrated that the entire spectrum of left ventricular dysfunction that is produced in this animal preparation, from minimal impairment to overt congestive heart failure, is a function of myocardial infarct size.[1-3] Recent advances in the clinical therapy of congestive heart failure have been directed toward reducing the load against which the impaired left ventricle must contract.[4-6] This study was undertaken to determine whether long-term treatment with an angiotensin-converting enzyme inhibitor, captopril, and its attendant vasodilatation would favorably alter the relationship between infarct size and ventricular performance and survival. These data have been reported in detail elsewhere.[7, 8]

Methods

Mature (16 to 24 weeks old) female Wistar rats (West Jersey Biological Supply) were anesthetized with ether, intubated, then ventilated by a positive pressure respirator (Harvard Apparatus). After a left thoracotomy, the heart was exteriorized rapidly and the left coronary artery was ligated with a suture.[1, 2] There is a 40% to 50% mortality rate during the first 48 hr after ligation. With this procedure, 3 weeks later, a time by which necrotic myocardium has been completely replaced by scar tissue in the rat,[9] survivors were randomly given either tap water or captopril (2 g/liter of drinking water) and fed rat chow ad libitum.

Hemodynamic studies. Fourteen weeks after the initiation of therapy, hemodynamic studies were performed by methods described in detail previously.[3, 10, 11] After induction of anesthesia with ether, the trachea was cannulated and ventilation and anesthesia were maintained by a respirator connected in series to an ether drip apparatus. The right carotid artery and jugular vein were cannulated for continuous measurement of systemic arterial and right atrial pressures, respectively, and heart rate. The arterial catheter was advanced briefly into the left ventricle for measurement of systolic and end-diastolic pressures and maximum positive dP/dt, then withdrawn. A midsternal thoracotomy was performed, and an electromagnetic flow probe (2.5 mm id, Statham) was placed around the ascending aorta for continuous measurement of mean (cardiac output less coronary flow) and phasic (peak flow velocity and maximum acceleration of aortic blood flow) blood flows. A catheter was positioned in the left femoral vein to permit infusions. Cardiac and stroke volume (the quotient of cardiac output and heart rate) outputs and total peripheral resistance (the quotient of the difference between mean arterial and right atrial pressures and cardiac output) were indexed for body weight. Baseline values of pressures, heart rate, and flow variables were determined every 2 min over a stable 10 min period, then averaged.

To determine the maximal cardiac and stroke volume outputs attainable during a volume loading, a rapid infusion (40 ml/kg/min) of Tyrode's solution was delivered for 45 sec, during which time cardiac output increased to, then was sustained at a maximal level despite continued increases in right atrial pressure. After the return of all hemodynamic variables to baseline levels, the arterial catheter was advanced into the left ventricle and the volume loading procedure repeated to determine the end-diastolic pressure at which maximal flow occurred.

The heart was arrested with potassium chloride and a double-lumen catheter, inserted into the aorta and advanced into the left ventricle, was secured by a ligature around the atrioventricular groove. The right ventricle was incised to relieve any possible compression on the left ventricle. Two pressure-volume curves were generated within 10 min of cardiac arrest by the recording of pressure and infusion of saline at a rate of 0.68 ml/min. The left ventricle was then fixed at that volume which corresponded

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to 5 mm Hg on the pressure-volume curve and immersed in formalin for 24 hr. The left and right ventricles then were separated and weighed.

From the passive pressure-volume relationship, the end-diastolic volume at which maximal output was attained was determined (the end-diastolic pressure measured during the second volume loading in vivo was related to a volume in vitro from the pressure-volume relation) and combined with the maximal stroke volume attained during the volume loading in vivo to derive an index of ejection fraction.

Survival studies. Two weeks after the ligation procedure the 302 survivors were anesthetized with ether, a metal identification tag was attached to the nape of the neck, and an electrocardiogram was obtained with a previously described nine-lead system.[12] The animals were assigned to receive either placebo or captopril by a balanced-block randomization process that was stratified according to three arbitrary electrocardiographic groups: group I had a normal QRS complex without evidence of a pathologic Q wave in limb leads I or aVL; group II had a Q wave ($\geq$ 1 mV) in either leads I or aVL, yet maintained a precordial R wave total over 10 mV; and group III had both abnormal limb lead Q waves and a sum of precordial R waves that was 10 mV or less. This electrocardiographic classification was used to maintain a balance of infarct sizes between treatment groups; all subsequent survival analyses were based on the histologic determination of infarct size.

Animals were housed in clear polyethylene cages that were maintained on two racks, each of which abutted one side of a double-sided laminar flow unit (Germ Free Laboratories), and were allowed food and the assigned therapy (water or captopril, 2 g/liter of drinking water) ad libitum. Cages with animals assigned to placebo or captopril were placed on the rack alternately. Temperature and humidity were controlled and the room had a 12 hr light-dark cycle. Each animal was followed until death or for up to 1 year after the ligation procedure.

The animals were inspected daily for mortality and the date of death was recorded, the carcass weighed, and a gross postmortem examination performed. The heart and lungs were excised and placed in formalin. The survivors at 1 year after infarction were anesthetized with ether for pathologic examination and the heart was arrested with intravenous KCl.

Pathologic examination. The lungs were examined and graded for thoracic infections. The atria and great vessels were trimmed from the ventricles, the right ventricular free wall was dissected from the left ventricle, and both ventricles were weighed separately. The left ventricle was dehydrated in alcohol, cleared in xylene, and embedded in paraffin, and 30 μm thick sections were cut serially from base to apex. Every twentieth section (representing every 1 mm of length) was stained with Masson's trichrome from which hematoxylin was omitted. These serial sections were mounted on slides and projected at a magnification of 12$\times$. For each section, the length of scar and of noninfarcted muscle of the endocardial and epicardial surfaces was determined by planimetry. The percentage of the endocardial and epicardial surfaces that comprised fibrous scar was calculated as the sum of the infarct lengths divided by the sum of the circumferences for each surface times 100. Infarct size was expressed as the average of the percent fibrous scar of the endocardial and epicardial surfaces.

Statistical analysis

Hemodynamic studies. Results are expressed as mean $\pm$ 1 SEM, except in table 1 where the variance term is presented as $\pm$ 1 SD. Myocardial infarctions were classified as small ($\leq$30% of left ventricular circumference), moderate (>30% <45%), and large ($\geq$45%). This partitioning resulted in groups of infarcts that were comparable in size between therapies (table 1). Rats that underwent the ligation procedure but did not sustain a myocardial infarction were designated as the noninfarcted group. If a one-way analysis of variance determined that there were differences among the groups within each treatment, a t test was used to compare each group with infarcts to its respective group without infarcts by means of Bonferroni's t statistic for three planned comparisons.[13] Differences between the untreated and treated rats matched for infarct size were determined by unpaired Student's t test.

Survival studies. Log-rank tests were conducted to determine whether infarct size altered 1 year survival in the untreated rats. Log-rank tests were also performed to compare survival between untreated and captopril-treated rats for all of the noninfarcted and infarcted rats. Similar analyses also were performed separately for each of the three infarct size groups. Since potential differences in rates of thoracic infections could have altered group survival, animals with a consolidated thoracic infection involving greater that one-third of the lung volume or a diffuse thoracic infection without localization were treated as censored observations.

TABLE 1

Infarct size distribution in captopril-treated and untreated rats

	No infarct	Infarcted Small	Moderate	Large
Untreated				
n	23	11	20	10
Infarct size (%)	—	17.3	38.3	49.3
SD	—	±5.4	±3.9	±4.0
Captopril				
n	14	5	10	11
Infarct size (%)	—	18.0	38.3	49.7
SD	—	±8.4	±3.0	±4.4

Results are expressed as mean $\pm$ 1 SD.

Results

Hemodynamic studies

Body and ventricular weights (table 2). In the untreated rats, the body weights of the small and moderate infarct groups were lower ($p < .02$) than those of the noninfarcted group, whereas in the captopril-treated rats there were no differences in body weight among the groups. For comparably sized infarcts, however, there were no differences in body weight between the untreated and captopril-treated rats. Although the ratio of left ventricular weight to body weight remained unchanged with increasing infarct size in both untreated and captopril-treated rats, this ratio was significantly lower in treated rats when compared with untreated rats with comparably sized infarcts (except for the small infarct group). In contrast, there was a progressive rise in the ratio of right ventricular weight to body weight in the untreated rats such that the ratios for the moderate and large infarct groups were greater ($p <$ .05 and $p < .005$, respectively) than that for their respective noninfarcted groups; this progressive increase in right ventricular weight in relation to infarct

TABLE 2

Body and ventricular weights of captopril-treated and untreated rats with myocardial infarction

	No infarct	Infarcted		
		Small	Moderate	Large
BW (g)				
Untreated	337±9	299±10	306±9	313±10
Captopril	334±6	327±15	319±8	317±8
RV (mg)				
Untreated	201±9	199±9	225±15	316±26
Captopril	194±11	195±3	210±8	225±26[A]
LV (mg)				
Untreated	740±23	699±32	702±25	699±16
Captopril	674±28	729±50	647±33	626±26
RV/W (mg/g)				
Untreated	0.60±0.02	0.67±0.03	0.73±0.04	0.99±0.08
Captopril	0.58±0.03	0.60±0.07	0.68±0.04	0.70±0.07[A]
LV/W (mg/g)				
Untreated	2.20±0.05	2.33±0.06	2.30±0.06	2.22±0.07
Captopril	2.02±0.06[A]	2.23±0.11	2.03±0.10[A]	1.98±0.08[A]

Results are expressed as mean ± SEM.

BW = body weight; RV = right ventricular weight; LV = left ventricular weight.

[A]$p < .05$, captopril-treated vs untreated control.

size was not observed in the captopril-treated rats. A comparison between therapies revealed that the ratio of right ventricular weight to body weight of the captopril-treated rats with large infarcts was significantly less than that of the untreated rats with large infarcts.

Prethoracotomy pressures (table 3). In both the untreated and captopril-treated rats, left ventricular systolic and mean arterial pressures decreased with increasing infarct size to the extent that pressures in the moderate and large infarct groups on both regimens were lower ($p < .025$) than those of their respective noninfarcted controls. When untreated and treated rats with comparable infarct sizes were evaluated, the blood pressures of rats receiving captopril were lower than those of the untreated rats (except in the group with small infarcts). Left ventricular end-diastolic pressure increased with infarct size in the untreated rats, being significantly elevated in the groups with moderate ($p < .025$) and large ($p < .005$) infarcts compared with the noninfarcted group. In contrast, in captopril-treated rats, an increase in filling pressure was apparent only in the group with large ($p < .005$) infarcts. Also, the rats with large infarcts receiving therapy had significantly lower filling pressures than those with large infarcts that were untreated ($p < .05$). Although right atrial pressure did not change with increasing infarct size in rats receiving captopril, right atrial pressure was significantly higher in untreated rats with large infarcts compared with untreated rats without infarcts ($p < .005$). Although right ventricular pressures were not consistently obtained, a sufficient number of measure-

TABLE 3

Prethoracotomy pressures and heart rate in captopril-treated and untreated rats with myocardial infarction

	No infarct	Infarcted		
		Small	Moderate	Large
LVSP (mm Hg)				
Untreated	145±3	139±4	126±2	122±1
Captopril	128±4[B]	130±10	104±5[C]	103±3[C]
LVEDP (mm Hg)				
Untreated	4.8±0.6	4.6±0.6	10.0±1.9	27.1±2.0
Captopril	4.8±0.4	4.9±0.7	6.6±1.7	14.4±3.5[A]
+dP/dt (mm Hg·sec⁻¹)				
Untreated	15,867±825	17,272±700	9,980±552	8,442±530
Captopril	14,157±835	14,643±2,404	9,938±894	8,597±932
MAP (mm Hg)				
Untreated	125±3	121±3	114±2	110±2
Captopril	107±4[B]	112±12	88±6[C]	88±2[C]
RAP (mm Hg)				
Untreated	−0.4±0.2	−0.4±0.2	−0.2±0.3	1.6±0.8
Captopril	−0.1±0.4	−0.7±0.6	−0.3±0.3	0.8±0.7
HR (beats/min)				
Untreated	379±11	438±17	402±14	401±13
Captopril	384±12	396±16	361±8	382±9

Results are expressed as mean ± SEM.

LVSP = left ventricular systolic pressure; EDP = end-diastolic pressure; +dP/dt = maximum rate of rise of pressure; MAP = mean arterial pressure; RAP = right atrial pressure; HR = heart rate.

[A]$p < .05$; [B]$p < .01$; [C]$p < .001$, captopril-treated vs untreated control.

ments were made in the groups with moderate and large infarcts to warrant comparison. No significant differences in right ventricular systolic (31 ± 3 vs 32 ± 4 mm Hg) or diastolic (3.3 ± 0.9 vs 2.6 ± 0.8 mm Hg) pressures were observed between untreated (n = 13) and treated (n = 6) rats, respectively, with moderate infarcts. On the other hand, in the group with large infarcts right ventricular systolic pressures were elevated ($p < .02$) in untreated rats (55 ± 6 mm Hg, n = 5) compared with captopril-treated rats (33 ± 4 mm Hg, n = 5), although the end-diastolic pressures were not elevated (6.8 ± 3.2 vs 3.8 ± 1.1 mm Hg, respectively). Peak positive dP/dt decreased with increasing infarct size in both untreated and treated rats, attaining a significant difference in the groups with moderate ($p < .01$) and large ($p < .005$) infarcts. There were no differences in peak positive dP/dt between the captopril-treated and untreated rats with comparable infarct sizes. The heart rate of rats with and without captopril was not altered by infarction (except for an increase [$p < .01$] in untreated rats with small infarcts) and there were no differences in heart rate between the untreated and treated rats for any infarct size.

Baseline hemodynamics (table 4). The reduction in mean arterial pressure observed in closed-chest, captopril-treated rats compared with untreated rats with comparable infarct sizes was also observed after thoracotomy. Both cardiac and stroke volume indexes decreased with increasing infarct size in untreated and treated rats: the cardiac index of the groups with moderate and large infarcts was lower ($p < .025$) than that of their respective noninfarcted groups. At comparable infarct sizes, there were no differences in cardiac index or stroke volume index between the untreated and treated rats. Total peripheral resistance index was unchanged by infarction as both mean arterial pressure and cardiac index fell to the same extent with increasing infarct size. However, vascular resistance was decreased in captopril-treated rats compared with untreated rats matched for infarct size, since the mean arterial pressure of the treated rats was always lower and the cardiac index was not different from that of the untreated rats. Two ejection phase indexes of contractility, peak flow velocity and maximum acceleration of ascending aortic blood flow, declined with increasing infarct size to significant levels in the groups with moderate and large infarcts among both untreated and captopril-treated rats. There were no differences in these indexes of contractility between untreated and treated rats for any infarct size.

Ejection phase volumes (figure 1). When maximal left

TABLE 4

Baseline hemodynamic characteristics of captopril-treated and untreated rats with myocardial infarction

	No infarct	Infarcted: Small	Moderate	Large
MAP (mm Hg)				
Untreated	110±4	115±4	99±3	100±4
Captopril	89±5[C]	94±7[A]	75±4[C]	79±5[B]
CI (ml · min⁻¹/kg)				
Untreated	253±13	250±21	205±11	200±17
Captopril	272±15	263±15	217±19	192±17
SI (ml · kg⁻¹)				
Untreated	0.67±0.04	0.63±0.06	0.53±0.03	0.55±0.05
Captopril	0.73±0.05	0.66±0.04	0.63±0.06	0.54±0.06
TPRI				
Untreated	0.45±0.02	0.48±0.03	0.51±0.04	0.54±0.07
Captopril	0.34±0.02[B]	0.36±0.02[A]	0.36±0.03[B]	0.44±0.05
pQ (ml/min)				
Untreated	6.1±0.2	5.1±0.2	4.9±0.2	3.9±0.3
Captopril	6.2±0.2	6.2±0.5	4.4±0.4	3.6±0.3
ACC (g)				
Untreated	15.7±0.8	16.4±0.5	11.8±0.5	10.3±1.1
Captopril	16.1±0.8	15.7±1.9	10.5±1.2	9.1±0.9

Results are expressed as mean ± SEM.

MAP = mean arterial pressure, CI = cardiac index; SI = stroke volume index; TPRI = total peripheral resistance index (mm Hg · ml⁻¹/min · kg⁻¹); pQ = peak aortic blood flow velocity; ACC = maximum acceleration of aortic blood flow (gravitational units).

[A]$p < .05$; [B]$p < .01$; [C]$p < .001$, captopril-treated vs untreated control.

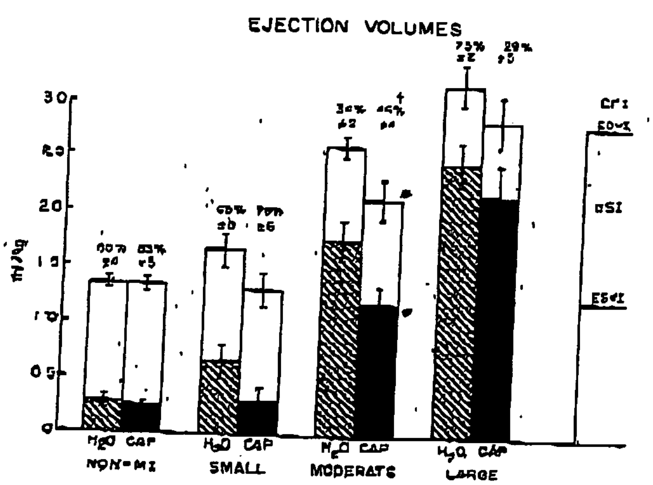

FIGURE 1. The ejection fraction volumes of untreated (H_2O) and captopril-treated (CAP) rats without infarcts (NON-MI) and with small, moderate, and large infarcts. The entire bar represents end-diastolic volume index (EDVI); the upper portion, peak stroke volume index (PSI); and the lower portion, end-systolic volume index (ESVI). Ejection fraction index (EFI) appears as a percentage above each bar. Results are expressed as mean ± SEM. *$p < .05$; †$p < .02$ captopril-treated rats vs untreated rats with infarcts of comparable size.

ventricular pumping ability was assessed during volume loading, the tendency for maximal stroke volume index to decline with increasing infarct size in the captopril-treated rats was similar to that in the untreated rats; decreases ($p < .005$) were observed in the groups with moderate and large infarcts compared with the respective noninfarcted groups. The end-diastolic volume indexes from which these forward outputs were ejected increased with increasing infarct size; however, this increase tended to be less marked in the captopril-treated rats so that the end-diastolic and end-systolic volume indexes of the treated rats with moderate infarcts was significantly lower ($p < .05$) than that of untreated rats with comparably sized infarcts. The ejection fraction index decreased with increasing infarct size, becoming less ($p < .005$) than that of the respective noninfarcted group in the untreated rats with small, moderate, and large infarcts and in the captopril-treated rats with only moderate and large infarcts. The tendency for the treated rats to eject forward outputs similar to, from filling volumes less than, those of untreated rats resulted in a trend to higher ejection fraction indexes for captopril-treated rats compared with untreated rats; this difference was significant for rats with moderate infarcts ($p < .02$).

Survival studies. These results have been censored for high-grade thoracic infections that were likely to account for death. The 1 year mortality for the untreated rats was increased ($p < .0001$) as a function of infarct size. The median survival for the noninfarcted rats and rats with small infarctions was greater than the 365 day observation period and therefore was undefined. Rats with moderate and large infarcts demonstrated reduced median survival durations of 228 and 184 days, respectively.

In the noninfarcted rats receiving captopril, survival was similar to that of the noninfarcted, untreated rats (figure 2, *A*). On the other hand, all captopril-treated rats with infarctions had a reduced 1 year mortality rate ($p = .01$) compared with untreated, infarcted rats. The median survival (all causes) for all of the untreated, infarcted rats was 197 days, whereas that for the captopril-treated, infarcted rats was 260 days. When survival was compared between therapies for each of the infarct size groups, it was improved in captopril-treated rats, although the difference was not always statisti-

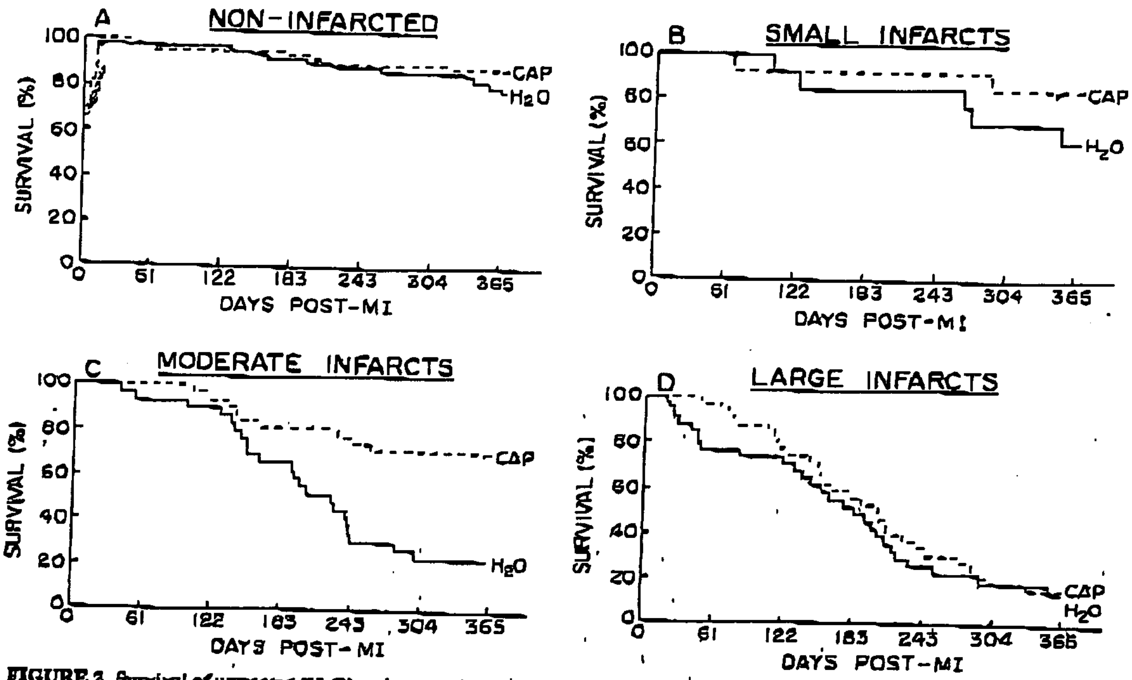

FIGURE 2. Survival of untreated (H_2O) and captopril-treated (CAP) rats without infarcts (*A*) and with small (*B*), moderate (*C*), or large (*D*) infarcts, using deaths with high-grade thoracic infections as censored observations (see text). With this censored analysis, the median survival for animals without infarcts (*A*) and with small infarcts (*B*), of both therapy groups was undefined (greater than the 365 day observation period). In rats with moderate infarcts (*C*) the median survival was 228 days and greater than 365 days for the untreated and captopril-treated animals, respectively. The median survival for rats with large infarcts (*D*) was similar in untreated (184 days) and captopril-treated (205 days) groups.

cally significant. There was no difference (p = .23) between therapies in overall 1 year mortality for rats with small infarcts (figure 2, B). In contrast, treated rats with moderate infarcts had a marked improvement (p = .02) in 1 year survival compared with untreated rats (figure 2, C); the median survival of treated rats was greater than 365 days compared with 228 days for the untreated rats. In rats with large infarcts receiving captopril, a long-term beneficial effect on survival was not sustained (p = .24) (figure 2, D); the median survival for treated rats was 205 days and for untreated rats 184 days.

Discussion

Captopril, an orally effective inhibitor of angiotensin-converting enzyme, has been shown to increase cardiac output and to reduce both pulmonary arterial wedge pressure and peripheral vascular resistance in selected patients with severe congestive heart failure.[14-19] For the most part, these clinical studies have been confined to patients with advanced congestive heart failure followed for relatively short periods of tim . There is, however, a paucity of information concerning the protracted effects of captopril therapy in less severe forms of heart failure.

In this study, the long-term hemodynamic and survival benefits of captopril were evaluated in rats with myocardial infarction presenting with a wide range of left ventricular dysfunction. As shown in our previous studies, ventricular performance in the healed phase of an experimental myocardial infarction was closely related to infarct size.[1-3] Four months after coronary artery ligation, rats with small infarcts had minimal alterations in baseline and volume-stressed hemodynamics. However, at this more protracted time after infarction, even rats with moderate-sized infarcts had a reduced baseline cardiac index and an elevated left ventricular end-diastolic pressure with respect to noninfarcted controls as well as a reduction in volume-stressed hemodynamics. Indexes of global ventricular contractile function (peak positive dP/dt, peak flow velocity, and maximum acceleration of aortic blood flow) also were depressed in rats with moderate infarcts. In rats with large infarcts there was a marked impairment in baseline and volume-stressed hemodynamics and in the indexes of ventricular contractile function.

The long-term administration of captopril, initiated 3 weeks after coronary artery ligation and continued for 3 months, resulted in a reduction in left ventricular and systemic arterial pressures and vascular resistance in both noninfarcted and infarcted rats. In noninfarcted rats and rats with small infarcts and normal ventricular performance, long-term captopril therapy did not alter ventricular pumping ability or contractile indexes. Indeed, even in rats with moderate and large infarcts with depressed contractile indexes, captopril did not further alter these assessments of the inotropic state (peak positive dP/dt, peak aortic flow velocity, and acceleration). Despite this apparent lack of inotropic effect of captopril, treated rats with moderate and large infarcts maintained forward output from a reduced operating diastolic pressure and volume compared with untreated rats with comparably sized infarcts. The prevention by captopril of the increase in right ventricular weight to body weight ratios observed in the untreated rats with moderate and large infarcts suggests that the reduced left ventricular filling pressure of the treated rats was sustained. The observation that left ventricular dysfunction is one of the most common causes of pulmonary hypertension, and thereby right ventricular hypertrophy, was made in the early studies of cardiac catheterization in man.[20] In our previous studies, right ventricular hypertrophy was consistently present 3 weeks after infarction in rats with large infarcts and elevated left ventricular end-diastolic pressures.[1-3] These rats with large infarcts had elevations in right ventricular systolic pressure that were proportional to the increases in left ventricular filling pressure. In the present study, captopril therapy was not initiated until 3 weeks after infarction and thus the absence of right ventricular hypertrophy in captopril-treated rats with large infarcts probably represents a true regression of right ventricular hypertrophy. Indeed, the long-term reduction of left ventricular filling pressure (and subsequently right ventricular systolic pressure) by captopril without a concomitant reduction in cardiac output may prevent the development of the chronic pressure overload and failure of the right ventricle that can occur in severe left ventricular dysfunction.

The improvement in ventricular performance and attenuation of left ventricular dilatation produced by long-term captopril therapy was associated with an improvement in survival rate. When therapy was instituted after the histologic resolution of the myocardial infarction, the infarcted animals receiving captopril had a prolonged 1 year survival rate compared with their untreated counterparts. The prolongation of survival postinfarction by an agent that improves ventricular performance and attenuates the deleterious remodeling of the left ventricle emphasizes the clos coupling between ventricular performance and survival. Of interest, in the rats with large infarcts and severe ventricular dysfunction, captopril failed to attenuate

ventricular dilatation significantly and was not associated with the prolongation of survival. On the other hand, the captopril-treated rats with moderate infarcts demonstrated the most striking improvement in hemodynamic profile and the greatest attenuation of ventricular dilatation; this group also exhibited the greatest prolongation of survival.

In the current management of patients with congestive heart failure, vasodilator therapy generally is reserved for those patients with advanced cardiac dysfunction in whom signs and symptoms of heart failure persist despite administration of cardiac glycosides and diuretics. This study in rats with myocardial infarction suggests that the salutary effects of long-term captopril therapy may be even more pronounced when initiated early in more moderate forms of heart failure.

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